Exhibit B

IN THE UNITED STATES DISTRICT COURT

FOR THE NORTHERN DISTRICT OF CALIFORNIA

OAKLAND DIVISION

PLEXXIKON INC.,

Plaintiff,

v.

NOVARTIS PHARMACEUTICALS CORPORATION,

Defendant.

Case No. 4:17-cv-04405-HSG

REBUTTAL EXPERT REPORT OF DR. ALEXANDER J. BRIDGES

Ctrm: 2 – 4th Floor
Judge: Honorable Haywood S. Gilliam, Jr.

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I. INTRODUCTION AND BACKGROUND

1. I submit this report on behalf of Plaintiff Plexxikon Inc. ("Plexxikon"), which engaged me as a technical expert in this matter. My opinions on the ability to synthesize compounds following reaction schemes described in United States Patent Nos. 9,469,640 (the "'640 Patent") and 9,884,539 (the "'539 Patent") (collectively, the "Asserted Patents") and other matters on which I expect to testify to are set forth below. The opinions contained in my report are based on the information and data available to me as of the date of service of this report. If new data or information becomes available, I reserve the right to modify or change the opinions expressed herein based on any such information.

2. I understand that Novartis Pharmaceuticals Corporation ("Novartis"), the named defendant in this litigation, commissioned an expert report from Dr. Phil S. Baran concerning the validity of the claims of the Asserted Patents. I respond to certain of Dr. Baran's opinions throughout my report.

II. QUALIFICATIONS AND EXPERIENCE

3. I am currently a full-time consultant specializing in synthetic chemistry for a number of companies and research universities, including BioMarin Pharmaceuticals Inc., Oncopia Therapeutics, Inc., and, previously, Oncofusion Therapeutics Inc. and JBR Pharma Inc. Prior to becoming a full-time consultant, I held a number of roles in pharmaceutical companies. Between 2003 and 2008, I served as Director and Senior Director of Preclinical Sciences at Quatryx Pharmaceuticals Inc. Between 2000 and 2003, I served as Oncology Discovery Executive Director, Interim Oncology Discovery Director, and Director of Cancer Chemistry at Pfizer Global Research and Development. I worked at Parke-Davis Pharmaceutical Research Division between 1984 and 1998 and again between 1992 and 2000, holding a number of positions, including Director of Diabetes Chemistry. In between these two periods at Parke-Davis, I was a Senior Scientist at Eisai Research Institute of Boston.

4. I also hold and have held a number of academic positions. I was an Associate Professor of Organic Chemistry at Northern Illinois University from 1978 until 1984, and have been an Adjunct Assistant Professor at Wayne State University in the Department of Chemistry since 1996 and an Adjunct Associate Professor at the University of Michigan in the School of Pharmacy since 2000. I am a member of the Royal Society of Chemistry, the American Chemical Society, Sigma Xi, and the American Association for the Advancement of Science. I am an author on more than 60 publications and

more than 20 book chapters and reviews, and am a named inventor on more than 30 issued U.S. patents and a number of patent applications.

5. I took a first-class honours degree in Chemistry from Oxford University in 1972, and was awarded a D Phil in Chemistry from the same university in 1974 under the supervision of Dr Gordon H. Whitham. I performed post-doctoral research with Professor J B Jones at the University of Toronto from 1976 to 1978.

6. A current copy of my Curriculum Vitae is attached to this report as Exhibit 1.

III. COMPENSATION AND PRIOR EXPERT TESTIMONY

7. I am being compensated for my work in this matter at my usual rate of $325 per hour. I am also being reimbursed for reasonable and customary expenses associated with my work and testimony in this matter. No part of my compensation depends on my opinions or on the outcome of this matter.

8. I have served as an expert witness prior to this matter, and a list of matters in which I have provided expert testimony at trial or deposition since 2013 is attached as Exhibit 2. A list of documents reviewed in connection with this report is attached as Exhibit 3.

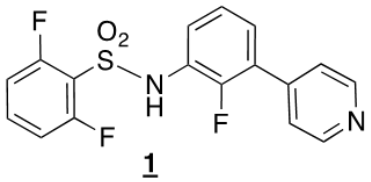
IV. SUMMARY OF OPINIONS

9. Compounds of Formula Ic and Formula Ie set forth in the Asserted Patents can be prepared via a Suzuki reaction following the steps set forth in "Scheme 2," in combination with the knowledge of a person of ordinary skill in the art.

10. A person of ordinary skill in the art ("POSITA") in 2005 would have been able to successfully perform to form the biaryl carbon-carbon bond described in "Scheme 2" without excessive experimentation.

11. To demonstrate that a POSITA could have successfully performed such a Suzuki reaction in 2005, I directed scientists at Adesis, Inc. to synthesize two compounds falling within the scope of Formula Ic and Formula Ie using Suzuki coupling reactions similar or identical to those exemplified in "Scheme 2" using materials and methods available to a POSITA in 2005. These two compounds are *N*-(2-Fluoro-3-(pyrid-4-yl)phenyl)-2,6-difluorobenzenesulfonamide (hereinafter "compound **1**") and *N*-[3-

[5-(2-aminopyrimidin-4-yl)-2-tert-butyl-1,3-thiazol-4-yl]-2-fluorophenyl]-2,6-difluorobenzenesulfonamide (hereinafter "compound **2**"):



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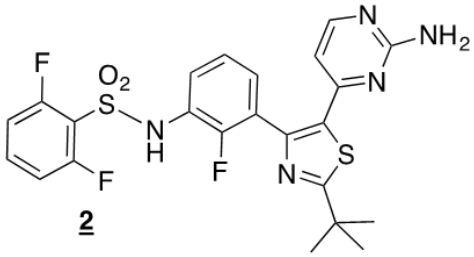

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12. Compounds **1** and **2**, both of which include a carbon-carbon bond connecting the fluorinated inner phenyl ring with a five- or six-membered ring containing nitrogen, were successfully synthesized following the steps outlined below.

V. DEFINITION OF A PERSON OF ORDINARY SKILL IN THE ART

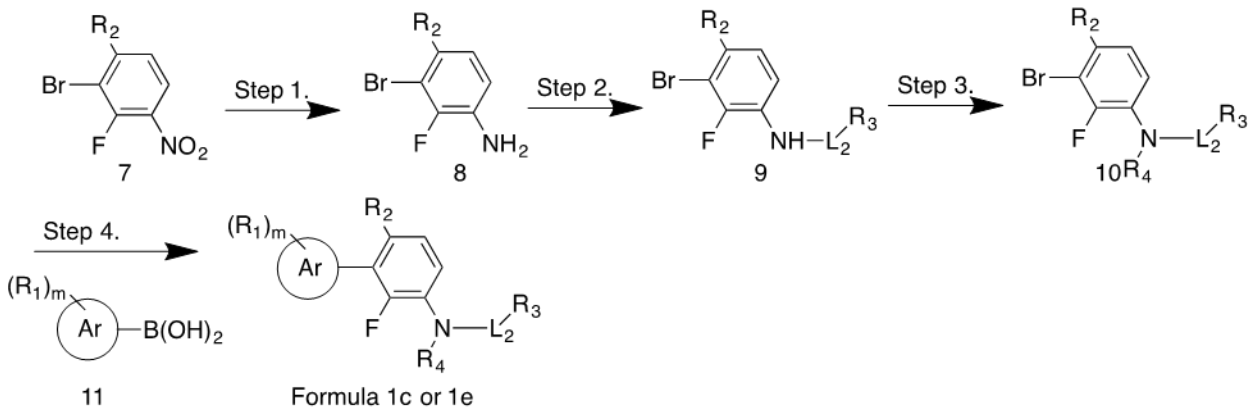
13. A person of ordinary skill in the art ("POSITA") would have a Ph.D. or equivalent degree in organic or medicinal chemistry and 2–3 years of post-graduate experience working in medicinal chemistry, synthetic organic chemistry, and/or kinase chemistry, including the development of potential drug candidates. A person of ordinary skill in the art would also include a person who has a Bachelor's or Master's degree in organic chemistry or medicinal chemistry if such a person had more years of experience in medicinal chemistry and/or the development of potential drug candidates.

VI. TECHNOLOGICAL BACKGROUND

A. Disclosures in the Asserted Patents

14. "Example 2" in the '640 Patent (described between column 70, line 71 and column 71, line 70 of the specification) describes the synthesis of compounds of Formulae Ic or Ie.[1] The '640 Patent explains that "Compounds of Formula Ic or Ie, as defined in paragraphs [0015] and [0021], respectively, can be prepared in four steps, as described in Scheme 2." "Scheme 2" is set forth below:

[1] The disclosures of the '640 Patent and the '539 Patent are identical.



15. The '640 Patent then describes in column 71 the synthesis of Compounds 8, 9, and 10, as well as the final synthesis "of Compound[s] of Formula 1c or 1e":

Step 1—Synthesis of Compound 8

Compound 7 (R^2 as defined in paragraph [0005]) is dissolved in an appropriate solvent (e.g. methanol). To this solution is added catalyst (e.g. palladium on carbon). The suspension is then placed under a hydrogen atmosphere and shaken at room temperature for over 12 hours. The catalyst is removed by filtration on a pad of celite and washed with an appropriate solvent (e.g. methanol). The filtrate is concentrated under reduced pressure to give compound 8, which is used in the next step without further purification.

Step 2—Synthesis of Compound 9

To compound 8 in an organic solvent (e.g. dichloromethane) is added a base (e.g. pyridine) followed by an appropriate acylating agent, isocyanate, or sulfonyl chloride. The reaction mixture is stirred at room temperature for over 12 hours. The reaction mixture is then poured into water. The organic layer is collected and the aqueous layer is extracted with an appropriate organic solvent (e.g. dichloromethane). The organic solvents are then combined. The desired compound 9 (L_2 and R^3 as defined in paragraph [0005], or L_2 is $S(O)_2$ for Formula Ic) is purified by chromatography.

Step 3—Synthesis of Compound 10

To compound 9 in an organic solvent (e.g. tetrahydrofuran or dichloromethane) is added a base (e.g. sodium hydride) at low temperature, followed by an appropriate alkylating agent (e.g. halide). The reaction mixture is stirred at room temperature or heated in an oil bath as necessary, for a few hours. The reaction mixture is then poured into water. The organic layer is collected and the aqueous layer is extracted with an appropriate organic solvent (e.g. ethyl acetate or dichloromethane). The organic solvents are then combined. The desired compound 10 (R^4 as defined in paragraph [0005]) is purified by chromatography.

Step 4—Synthesis of Compound of Formula Ic or Ie

A mixture of compound 10, an appropriate boronic acid 11 (Ar, m and R^1 as defined in paragraph [0004]), and a catalyst (e.g.

tetrakis(triphenylphosphine)palladium) in a mixture of base (e.g. aqueous solution of potassium carbonate) and an appropriate organic solvent (e.g. acetonitrile) is heated in an oil bath or is irradiated in a microwave system at over 100° C. for an appropriate time depending on starting materials. The reaction mixture is poured into water and then extracted with an appropriate organic solvent (e.g. dichloromethane or ethyl acetate). The organic solvents are then combined. The desired compound of Formula Ic (L_2 is $S(O)_2$) or Id is purified by chromatography.

16. "Step 4" described above is what is commonly known as a Suzuki, or sometimes Suzuki-Miyaura, coupling reaction, which I describe below.

B. Relevant Suzuki Coupling Literature

17. The Suzuki coupling reaction to form biaryl compounds by combining an aryl boronic acid derivative and an aryl halide (or a pseudohalide such as triflate), typically in the presence of a palladium phosphine complex catalyst, is a technique that is widely used in synthetic chemistry. The reaction traces its name back to a 1981 publication from Suzuki et al., *The Palladium-Catalyzed Cross-Coupling Reaction of Phenyl-boronic Acid with Haloarenes in the Presence of Bases*, Synth. Commun. 11, 513–19 (1981). Professor Suzuki was awarded the Nobel Prize in Chemistry for discovering this reaction in 2010.

18. Suzuki coupling reactions were well established in 2005, and would have been known to a POSITA as of that date. A search using SciFinder, a comprehensive database for chemical literature produced by Chemical Abstracts Service, reveals that at the end of 2005, a POSITA would have had available to him or her at least 2,400 examples of Suzuki coupling reactions in research articles and patent papers dating back to the original 1981 publication, along with at least 150 review articles in academic journals discussing Suzuki coupling reactions. Based on the years since the original Suzuki paper was published and the amount of peer-reviewed and other publications concerning the reaction, it is my opinion that a POSITA in 2005 would have had at least a moderate familiarity with the Suzuki coupling reaction.

19. I set out to synthesize two compounds with Formulae Ic and Ie of the Asserted Patents using Suzuki coupling methods known to a POSITA in 2005. Dr. Baran opines in paragraphs 364 and 365 of his report that, for a compound like dabrafenib, the presence of an acidic sulfonamide on the aryl bromide to be Suzuki-coupled greatly decreases the probability that the Suzuki coupling reaction will

occur, and further opines that the fluorine atom adjacent to the bromine atom to be coupled will in fact make the reaction even more unlikely. To address these opinions, I first prepared an aryl bromide containing all of these components to demonstrate that I could make such a compound undergo a Suzuki coupling reaction with a heteroaryl boronic acid without requiring excessive experimentation. My first synthesis, that of compound **1**, described below, follows Scheme 2 of the '640 Patent, coupling *N*-(3-bromo-2-fluorophenyl)-2,6-difluorobenzenesulfonamide **5** with pyridine-4-boronic acid **6** using the Suzuki coupling conditions precisely as suggested in the patent.

20. I also synthesized dabrafenib, a more complicated compound falling within the scope of Formulae Ic and Ie, using the methodology outlined in the Asserted Patents in combination with materials available to a POSITA in 2005. My synthesis of dabrafenib—i.e., compound **2**—was accomplished via a short, practical route, involving coupling the heteroaromatic moiety to the phenylsulfonamide moiety via a Suzuki coupling reaction, forming exactly the same carbon-carbon biaryl bond as set forth in Scheme 2.

21. In preparing for the synthesis of compound **2**, I was cognizant of four concepts, all of which would have been obvious to a POSITA in 2005 setting out to synthesize such a compound. First, Suzuki coupling reactions are frequently carried out using boronic esters rather than their corresponding boronic acids, in part because such boronic esters are frequently easier to synthesize than boronic acids.[2] This is especially true for the so-called "pinacolylboranes," one of which would be used in the synthesis of compound **2**. I therefore determined that I would examine a Suzuki coupling reaction based-route using a pinacolyl borate ester rather than a pinacolyl boronic acid. However, as explained below, I in fact accomplished the Suzuki coupling with the boronic acid.

22. Second, based on publications available in 2005, tetrakis(triphenylphosphine)palladium was known not to be the most effective catalyst for use in Suzuki coupling reactions. A review of pre-2005 publications suggested that [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II)dichloride ("$PdCl_2$(dppf)") was known to be a convenient and popular catalyst with superior activity in Suzuki

[2] *See* J. Org. Chem. 60, 7508 (1995); J. Org. Chem. 62, 6458 (1997).

couplings, and I therefore used this catalyst in my synthesis of compound **2**.[3] Dr. Baran opines in paragraph 357 of his report that "the palladium catalyst described in P2 is the most primitive catalyst available for running Suzuki reactions," and that "using newer, more sophisticated catalysts" could enable such reactions to occur, although he opines that "such reactions would be very difficult." Based on this literature and on our successful synthesis of compound **2**, a complex molecule, I disagree that such a Suzuki coupling reaction would have been difficult or outside the skill of a POSITA in 2005.

23. Third, I, like Dr. Baran, noted the relative dearth of azaaromatic (i.e., carbon rings with one or more nitrogen atoms) boronic acids and boronate esters described in pre-2006 publications. These publications, however, did not provide an explanation for the absence of these molecules. In my opinion, the relative lack of mentions of such boronic acids and esters is attributable to the fact that POSITAs generally could have found simpler ways to solve problems encountered in the field. Aryl boronate esters and boronic acids are frequently made from their corresponding aryl bromides, and the Suzuki coupling reaction in the ensuing step of a biaryl synthesis, required for the preparation of compound **2**, typically involves coupling the boronic acid/boronate with an aryl bromide. Thus, the overall process frequently involves aryl bromide A being converted to aryl boronate A', and then coupling aryl A' with aryl bromide B to form the biaryl aryl A-aryl B, replacing two carbon-bromine bonds on two aryl rings with a single carbon-carbon bond between the two rings. If a POSITA were concerned about the perceived difficulty of synthesizing aryl boronate A', he or she would know to reverse which of the two aryl rings to boronate, and then perform the Suzuki coupling step—that is, borylate aryl bromide B to form aryl boronate B', and then couple aryl B' with aryl bromide A to form the same biaryl aryl A-aryl B. Using such a reversal does not involve any extra steps, and would have been obvious to any experienced graduate student, and second nature to any POSITA.

24. Fourth, although the Suzuki coupling reactions depicted in Example 2 of the Asserted Patents involve reacting aryl halides with heteroaryl boronic acids, it was well known to POSITAs in 2005 that the halide and boronic acid intermediates could be reversed, such that the halogen is part of the

[3] *See* Tetrahedron Letters 46, 6529 (2005); J. Org. Chem. 70, 4188 (2005), $PdCl_2$(dppf) has also been shown to be a very good cross coupling catalyst in the trifluoroborate modification of the Suzuki coupling. *See* J. Org. Chem. 68, 4302 (2003); Tetrahedron Letters 40, 213 (1999); J. Org. Chem. 70, 4188 (2005).

heteroaryl coupling partner and the boronic acid is part of the aryl coupling partner. Indeed, this reversal was taught by a number of the references cited by Dr. Baran, as explained in paragraphs 168 through 176 of the expert report of Dr. Jeffrey Winkler, and further examples will be discussed later in this report. Thus, a POSITA would have known that, if either component in the Suzuki coupling reaction (the aryl halide or heteroaryl boronic acid derivative of interest) were suspected of being difficult to make or unstable, the reaction could most likely be accomplished in a straightforward manner, by reversing the roles of the two coupling partners and reacting an aryl boronic acid derivative with a heteroaryl halide.[4] As aryl bromides are commonly used as precursors to the corresponding boronic acids, in many syntheses this would not add any extra steps to the reaction sequence—one would simply carry out the borylation on the aryl bromide, and then couple the resultant boric acid derivative with the heteroaryl bromide, instead of borylating the heteroaromatic bromide, and then performing the Suzuki coupling with the aryl bromide.

25. To further establish that a POSITA in 2005 would have known he or she could have reversed the bromide and boronic acid in a Suzuki coupling reaction, I reviewed SciFinder search results for 2-, 3-, and 4-phenylpyridines made using Suzuki coupling reactions up to the end of 2005 by either of two schemes: (1) coupling a pyridine boronic acid derivative with an aryl halide, as suggested in Scheme 2 of the Asserted Patents; or (2) a coupling a phenylboronic acid derivative with a pyridyl halide, which a POSITA would have understood to be an example of the "reverse" Suzuki coupling strategy described in the previous paragraph. By the end of 2005, there were at least 32 publications describing the synthesis of 2-phenylpyridines via a phenylboronic acid-pyridyl halide Suzuki coupling reaction,[5] at least 10

[4] Canadian J. Chem. 79, 1827 (2001).

[5] *See, e.g.*, Heterocycles 26, 2711 (1987); SynLett 45 (1999); J. Molecular Catal. A 152, 69 (2000); Tetrahedron Letters 42, 639 (2001); Chemical Communications 2408 (2001); Tetrahedron Letters 42, 5659 (2001); J. Organometallic Chem. 663, 46 (2002), EP 1167372 (2002); Organic Letters 4, 3529 (2002); Japan Patent App. 2002249483; J. Organometallic Chem. 687, 327 (2003); Organic Biomol. Chem. 1, 1643 (2003); WO 2003/013723; WO 2003/045941; Angew Chem. Int. Edn. 42, 1407 (2003); Organic Letters 5, 953 (2003); J. Organic Chem. 68, 5660 (2003); Studies in Surface Sci. Catal. 145, 541 (2003); J. Organic Chem. 68, 9412 (2003); Green Chemistry 6, 53 (2004); New J. Chemistry 28, 600 (2004); US 2004/0147392; Advanced Synthesis & Catalysis 346, 1798 (2004); Chemical Communications 1922 (2004); J. Organic Chem. 69, 3173 (2004); Chimica Oggi 23, 10 (2005); Tetrahedron 61, 7438 (2005); Tetrahedron 61, 12065 (2005); J. Organometallic Chem. 690, 3963 (2005); Organic Letters 7, 1829 (2005); Tetrahedron Letters 46, 3205 (2005); Organic Letters 7, 4907 (2005).

publications describing the synthesis of 4-phenylpyridines via a phenylboronic acid-pyridyl halide Suzuki coupling reaction,[6] and at least 46 publications describing this coupling for 3-phenylpyridines.[7] However, there were no publications describing the synthesis of 4-phenylpyridines by coupling a pyridylboronic acid derivative with a phenyl halide by the end of 2005, and only one reference each to the synthesis of 2-phenylpyridines[8] and 3-phenylpyridines[9] via a pyridylboronic acid. This suggests that a POSITA in 2005 would have understood he or she could exchange the bromide and boronic acids in a Suzuki coupling of an aromatic bromide with a heteroaryl boronic acid derivative, and would have had a considerably higher expectation of success by executing this simple exchange of roles for the two coupling partners in the Suzuki reaction.

26. I understand that Dr. Baran opines in paragraph 362 of his report that "thiazole-based boronic acid reagents are extremely difficult to prepare and are well-documented to fail in Suzuki reactions," and that "4-thiazolyl boronic acids are notorious for being the most difficult out of all possible thiazole isomers in this regard." If this were true, however, a POSITA would have known *ex ante* that 4-thiazole boronic acids are difficult coupling partners, and would therefore have reversed the coupling

[6] *See, e.g.*, Heterocycles 26, 2711 (1987); SynLett 45 (1999); J. Organometallic Chem. 663, 46 (2002). J. Organometallic Chem. 687, 327 (2003); Tetrahedron Letters 42, 5659 (2001); J. Organic Chem. 68, 9412 (2003); Japan Patent App. 2003128641; J. Organic Chem. 69, 3173 (2004); Organic Letters 6, 3337 (2004), J. Organic Chem. 68, 9412 (2003).

[7] *See, e.g.*, Heterocycles 26, 2711 (1987); Tetrahedron Letters 32, 2273 (1991); Tetrahedron 48, 8117 (1992); Angew Chem. Int. Edn. 39, 4153 (2000); Synthetic Communications 30, 3501 (2000); Chemical Communications 325 (2001); Tetrahedron Letters 42, 635 (2001); Tetrahedron Letters 42, 5659 (2001); Tetrahedron Letters 42, 6523 (2001); WO 2001/086572; Tetrahedron Letters 42, 9099 (2001); Angew Chem. Int. Edn. 41, 179 (2002); Angew Chem. Int. Edn. 41, 1521 (2002); Organic Letters 4, 3371 (2002); Organometallics 21, 5470 (2002); J. Organometallic Chem. 663, 46 (2002); Organic Letters 4, 3529 (2002); Japan Patent App. 2002249483; J. Organometallic Chem. 687, 327 (2003); Chemical Communications 2652 (2003); Organic Biomol. Chem. 1, 1643 (2003); Tetrahedron Letters 44, 7537 (2003); Studies in Surface Sci. Catal. 145, 541 (2003); J. Organic Chem. 68, 7733 (2003); J. Organic Chem. 68, 9412 (2003); Japan Patent App. 2003128641; WO 2003/013723; Chemical Communications 38 (2004); Advanced Synthesis & Catalysis 346, 1742 (2004); J. Organic Chem. 69, 3173 (2004); Advanced Synthesis & Catalysis 346, 1798 (2004); Advanced Synthesis & Catalysis 346, 1812 (2004); Organic Letters 6, 2305 (2004); Japan Patent App. 2004189705; WO 2004/101581; Chimica Oggi 23, 10 (2005); Tetrahedron Letters 46, 3205 (2005); SynLett 2057 (2005); Angew Chem Int Edn 44, 2444 (2005); J. Organometallic Chem. 690, 3963 (2005); J. Amer. Chem. Soc. 127, 10045 (2005); Tetrahedron 61, 9767 (2005); US 2005/0215804; Tetrahedron 61, 12065 (2005); Tetrahedron 61, 12121 (2005).

[8] Tetrahedron Letters 45, 685 (2004).

[9] SynLett 2057 (2005).

partners, creating a 4-thiazole bromide that would be coupled with a boronic acid. This is a common practice in medicinal chemistry, and minimal, if any, experimentation would have been expected on the part of the POSITA. Both thiazole-4-boronic acid and thiazole-5-boronic are known compounds, and are mentioned in prior art patent applications for Suzuki couplings,[10] although neither application gives any experimental details. Currently, thiazole-4-boronic acid has 65 listed vendors in the SciFinder database, and its pinacol ester has 63 listed vendors. The corresponding vendor numbers for thiazole-5-boronic acid and its pinacol ester are 130 and 34, respectively. The main use for all four of these compounds is presumably in Suzuki coupling reactions. Therefore, one cannot assume that the coupling exactly as shown in Scheme 2 does not work; I simply chose to go another way using the same technology.

27. One of the advantages of the use of bis(pinacolyl)diborane and $PdCl_2$(dppf) in borylations of (hetero)aryl halides (and triflates) is that the reaction is often clean enough, and results in high enough yields, that at the completion of the borylation step one can simple add a second (hetero)aryl bromide to the reaction mixture, optionally add more catalyst at the same time, and run the Suzuki coupling to give a "one pot" synthesis of asymmetric biaryls.[11] An interesting variant on this technique is the use of these conditions to dimerize (hetero)aryl halides or triflates via these Suzuki-Miyaura conditions.[12] In some cases, the initial borylation takes place with a weaker base like potassium acetate, and the subsequent Suzuki reaction is triggered by adding a stronger base such as potassium phosphate.[13] Although I did not make use of this strategy, it demonstrates further the fluidity between components in the Suzuki coupling, and the fact that a POSITA would have had many strategies to choose from in making compounds **1** and **2** following Scheme 2 in the Asserted Patents.

28. Indeed, it was well known by 2005 that brominated thiazoles could be used in Suzuki coupling reactions, including with 4-bromothiazoles to form 4-arylthiazoles.[14] For example, based on a

[10] *See* WO 2003.047577, WO 2002/083111.

[11] *See, e.g.*, Synthesis 1681 (2001).

[12] *See* Tetrahedron Letters 44, 4895 (2003); J. Org. Chem. 68, 3729 (2003).

[13] *See* Organic & Biomolecular Chem. 1, 2084 (2003).

[14] Other halides, such as iodide and chloride, can be used to perform Suzuki coupling reactions. Generally speaking, the reactivity order for the halide portion of a Suzuki coupling reaction is that iodide is a better substrate than bromide, chloride is less reactive than iodide or bromide, and fluorides do not

review of SciFinder search results up to the end of 2005, at least 14 peer-reviewed papers published in or before 2005 describe the creation of 2-phenylthiazoles using arylboronic acids to make 2-, 4-, and 5-aryl-substituted thiazoles.[15] At least two journal articles describing the Suzuki coupling of arylboronic acid derivatives with 5-bromothiazoles were also published in or before 2005,[16] and no fewer than four journal articles describing the Suzuki coupling of arylboronic acid derivatives with 4-bromothiazoles were published in or before 2005.[17] Moreover, at least 74 prior art patent publications describe 2-bromothiazole couplings,[18] at least 15 patent publications describe 5-bromothiazole couplings,[19] and at least 6 patent publications describe 4-bromothiazole couplings.[20]

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undergo these reactions. On the other hand, chlorides are the most available halides and bromides are likewise quite easy to obtain, whereas iodides are generally less available and frequently less stable.

[15] *See, e.g.*, Tetrahedron Letters 26, 5997 (1985); Tetrahedron Letters 41, 1707 (2000); Chemistry Eur. J. 6, 2874 (2000); Bioorg. Med. Chem. Lett. 12, 471 (2002); J. Org. Chem. 67, 7541 (2002); Organic Letters 4, 1363 (2002); J Organomet. Chem. 687, 327 (2003); Organic Letters 5, 2911 (2003); Heterocycles 59, 473 (2003); J. Org. Chem. 68, 4302 (2003); J. Med. Chem. 48, 224 (2005); Tetrahedron 61, 12121 (2005); Medicinal Chemistry 1 601 (2005); Nucleosides Nucleotides & Nucleic Acids 24, 571 (2005); Bioorg. Med. Chem. Lett. 16, 49 (2006) [E-published October 2005].

[16] *See, e.g.*, Organic Letters 4, 1363 (2002); Tetrahedron Letters 45, 7157 (2004).

[17] *See, e.g.*, Tetrahedron Letters 41, 1707 (2000); Organic Letters 4, 1363 (2002); J. Med. Chem. 48, 7520 (2005); Bioorg. Med. Chem. Lett. 16, 49 (2006) [E-published October 2005].

[18] *See, e.g.*, WO 1998/028264, WO 1998/050358, WO 1998/049152, WO 1998/046582, WO 1999/019300, WO 1999/018941, WO 1999/066925, WO 1999/053039, WO 2000/000487, WO 2001/034135, WO 2001/034137, WO 2001/034197, WO 2001/034198, WO 2001/034580, WO 2001/055111, WO 2001/090108, WO 2002/002551, WO 2002/014311, WO 2002/015662, WO 2002/016355, WO 2002/017358, WO 2002/024636, WO 2002/034745, WO 2002/048134, WO 2002/068439, WO 2002/074758, WO 2002/074773, WO 2002/083673, US 2002/0193405, Ger. Offen. 10,114,970, WO 2003/007945, WO 2003/010141, WO 2003/011842, WO 2003/022842, WO 2003/037274, WO 2003/037332, WO 2003/040147, WO 2003/050132, WO 2003/072102, WO 2003/087057, WO 2003/089418, WO 2003/093252, WO 2004/002977, WO 2004/006922 , WO 2004/006923, WO 2004/006924, WO 2004/007493, WO 2004/012684, WO 2004/022526, WO 2004/024081, WO 2004/041279, WO 2004/043458, WO 2004/058762, WO 2004/060281, WO 2004/063155, WO 2004/063190, WO 2004/065367, WO 2004/072025, WO 2004/078169, WO 2004/092131, WO 2004/092521, US 2004/0082553, US 2004/0092521, US 2004/0106621, Ger. Gebr. 20,217,570, Ger Offen. 10,300,398, WO 2005/007087, WO 2005/019151, WO 2005/019161, WO 2005/058848, WO 2005/060963, WO 2005/087746, WO 2005/100301, WO 2005/113522, WO 2005/118535, JP 2005/132834.

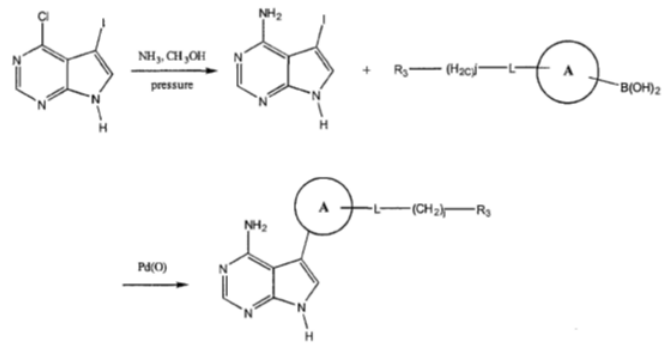
[19] *See, e.g.*, US 5,750,549, WO 2001/017995, WO 2003/004509, WO 2003/007945, WO 2003/010141, WO 2003/011838, WO 2003/053925, WO 2003/072557, WO 2003/093252, WO 2004/016608, WO 2004/096822, WO 2005/058848, WO 2005/080382, WO 2005/116000, US 2005/0065178.

[20] *See, e.g.*, US 5,750,549, WO 2001/038326, WO 2001/090108, WO 2002/074758, US 2004/0058970, WO 2005/111003.

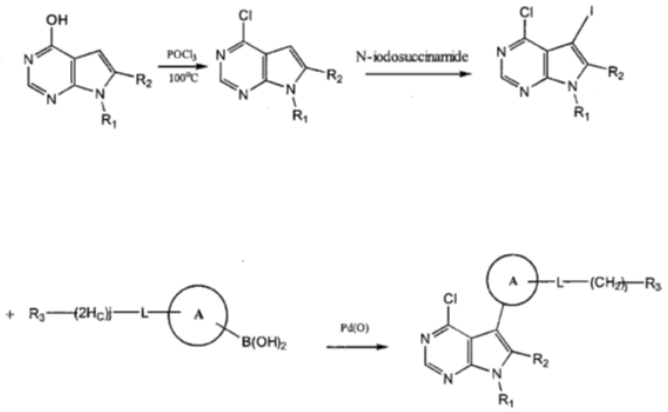
29. In total, there are around 100 references published in or before 2005 regarding making arylthiazoles via Suzuki coupling reactions on thiazoyl bromides, including nine that cover the biaryl bond that I proposed to form. A cursory search of the literature would have yielded examples of this process, and in my opinion would have encouraged a POSITA to adopt the synthesis strategy that I propose.

30. Dr. Baran opines in paragraph 345 of his report that the Suzuki coupling was originally developed to link "aryl, as opposed to heteroaryl moieties," but he fails to recognize that by 2005, the Suzuki coupling reaction was widely employed for coupling heteroaryl compounds. For example, one of the very references Dr. Baran relies on as purported prior art, BASF 1998[I],[21] uses Suzuki coupling chemistry, and literally trillions of compounds claimed in this reference are depicted in Schemes 2 and 3 as being made by a Suzuki coupling reaction between a heteroaryl halide and an aryl boronic acid derivative:

Scheme 2



Scheme 3

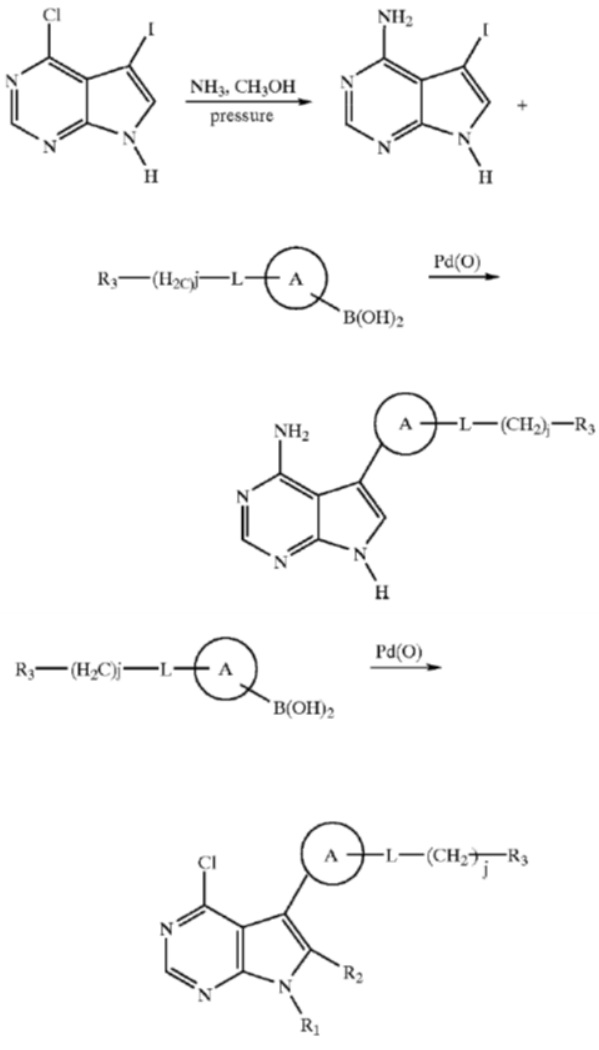


[21] PCT Patent Publication No. WO 00/017202.

31. In fact, even Example 1 in the experimental section of BASF 1998[I] involves borylation of a bromobenzene, containing an acidic hydrogen substituent, using bis-(pinacolato)diborane and $PdCl_2$(dppf), which is then used to couple with a heteroaromatic halide, to give a Suzuki reaction product in 81% yield based on the halide, which a POSITA would have looked on as a rather encouraging precedent.

32. A second reference on which Dr. Baran relies, BASF 1998[II],[22] also uses Suzuki coupling reactions between a heteroaryl and aryl. Schemes 2 and 3 from BASF 1998[II] are shown below, both of which depict such a Suzuki coupling:

Scheme 2



[22] PCT Patent Publication No. WO 00/17203.

33. In this patent application, Example 1 also uses a Suzuki coupling between an aryl boronate ester and a heteroaryl halide, although in this case the yield is not reported. However, in step (e) of Example 1, displacement of the 4-chlorine atom with ammonia is described, demonstrating again that my synthesis strategy was very well precedented.

34. Dr. Baran further opines in paragraph 364 of his report that the presence of a fluorine atom ortho to the bromine substituent would make the Suzuki coupling reaction unusually difficult. Notwithstanding our successful synthesis of compound **2**, a review of relevant literature as of 2005 suggests a POSITA would not have understood this to be the case. In order to probe this understanding, I ran searches on SciFinder using three search terms. First, I searched for instances in which a 2-fluorophenylboronic acid was converted to a 2-phenylfluorobenzene, with all other positions unspecified. This search returned more than 68,000 hits, the vast majority of which involved a Suzuki coupling reaction. I then looked at the conversion of simple phenylboronic acids to 2-phenylfluorobenzene, with all other positions unspecified, and obtained over 111,000 hits. Repeating the same search, but specifying that the 2- and 6-positions of the phenylboronic acid must be a hydrogen atom, I still ended up with over 38,000 hits. Finally, I looked at the conversion of 2-bromofluorobenzene into 2-phenylfluorobenzene, again with all other positions open. This generated about 72,000 hits. Even though a large number of these reactions might have been Stille and other types of couplings, over 31,000 of these reactions involved the use of sodium carbonate, potassium carbonate, potassium phosphate, cesium carbonate, or potassium acetate, all of which a POSITA would normally have associated with Suzuki coupling reactions. Moreover, although these search results were too large for me to analyze by year, I confirmed that each of these three searches returned pre-2006 publications, and some such prior art publications described high yields from the Suzuki coupling reactions. Based on the vast number of reactions described in SciFinder and the fact that all three searches I performed resulted in couplings described prior to 2006, in my opinion there would have been no reason for a POSITA in 2005 to have anticipated or expected that the presence of fluorine ortho to the bromine substituent would have prevented a POSITA from synthesizing compound **2** via a Suzuki coupling reaction.

35. I also note that Dr. Baran suggests in paragraph 347 of his report that the presence of unprotected acidic nitrogens in the compound might preclude the use of a Suzuki coupling reaction,

presumably because of the possibility such nitrogens may poison the catalyst, decompose other reactants, or lead to coupling at the acidic nitrogen, forming a new carbon-nitrogen bond rather than at the desired carbon atom. In 2005, compound **3**, one of the coupling partners used in the synthesis of compound **1**, was not described in the literature. Instead, I searched for the coupling of 3-bromosulfonanilides forming 3-phenylsulfonanilides, with all positions, including the substituent on the sulfonyl portion, being unspecified. This yielded four hits, all four of which involved the use of Suzuki couplings.[23] I then searched for the use of 3-sulfonamidophenyl boronic acids in the formation of 3-phenylsulfonanilides, again with all other positions unspecified. This search resulted in one pre-2006 peer reviewed publication, and up to 29 examples of the use of 3-(methylsulfonamido)phenylboronic acid in Suzuki coupling reactions prior to 2006 in the patent literature.[24] I discovered through these searches that the simple compound 3-(methylsulfonamido)phenylboronic acid is currently sold by around 100 vendors, suggesting that it has synthetic utility, presumably in Suzuki reactions. A POSITA in 2005 therefore would have had access to a number of examples showing that unprotected sulfonamide nitrogen atoms would not pose a problem in a Suzuki coupling, in addition to knowledge that sulfonamides generally were well tolerated in Suzuki coupling reactions prior to 2006.

36. Finally, Dr. Baran opines in paragraph 361 of his report that "the fact that the GSK scientists who made dabrafenib did not use a Suzuki reaction to form the compound" demonstrates that such a reaction is "nearly impossible to perform using the teachings of P2." The fact that GSK scientists used a different reaction scheme to synthesize dabrafenib has no bearing on whether such a reaction "is nearly impossible to perform using the teachings of P2." Of course, there could be many reasons why GSK's scientists chose an alternative synthetic route.

37. In sum, the chemical literature prior to 2006 would have been highly suggestive to a POSITA that compound **1** could be readily synthesized as described in Scheme 2 of the '640 Patent by using a Suzuki coupling between compounds **5** and **6**. The literature likewise would have suggested that

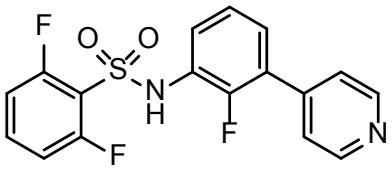
[23] *See* WO 1998/042670; WO 2004/010943; WO 2004/011427; WO 2005/04296.

[24] *See, e.g.*, US 2004/0152736; US 2005/0054640; US 2005/0267105; WO 2001/056990; WO 2001/096330; WO 2003/022852; WO 2003/072561; WO 2004/052847; WO 2004/058759; WO 2004/071447; WO 2004/076412; WO 2005/014566; WO 2005/051324; WO 2005/063766; WO 2005/066163; WO 2005/067923; WO 2005/096784; WO 2005/097740; WO 2005/110410.

analogous coupling reversing the bromine and boronic acid would have permitted the successful synthesis of compound **2**. Indeed, the Suzuki coupling between compounds **10** and **11** had excellent support prior to 2006, and would have been expected to result in a successful synthesis without excessive experimentation.

VII. SYNTHESIS OF COMPOUND 1

38. At my direction, scientists at Adesis, Inc. synthesized *N*-(2-Fluoro-3-(pyrid-4-yl)phenyl)-2,6-difluorobenzenesulfonamide, which has the following chemical structure:



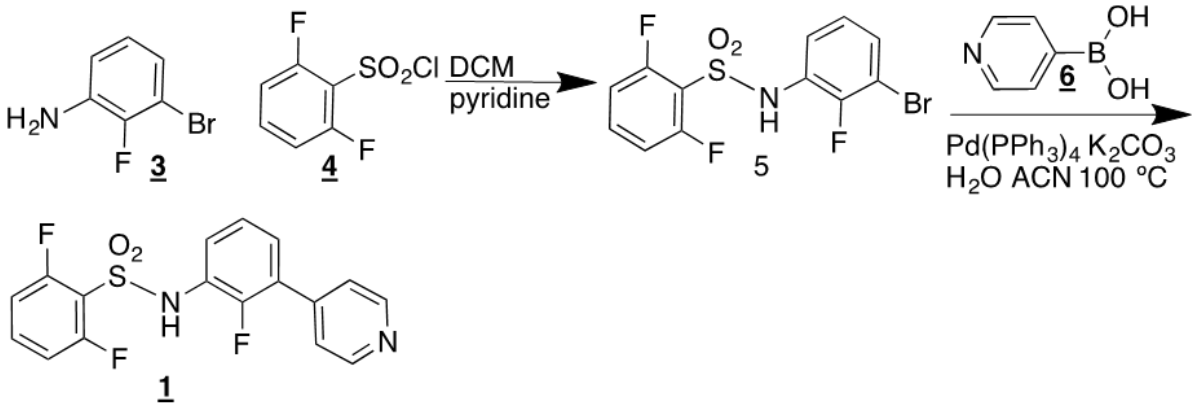
1

Compound 1: *N*-(2-Fluoro-3-(pyrid-4-yl)phenyl)-2,6-difluorobenzenesulfonamide

39. Except where expressly noted otherwise, all reagents used in the synthesis were commercially available in 2005, and were obtained from the sources set forth in Appendix A.

A. Synthetic Scheme for Compound 1

40. An overview of the synthetic scheme I followed to synthesize compound **1** is below, with reactants and intermediaries referred to by compound number:



41. Both 3-bromo-2-fluoroaniline **3** and 2,6-difluorobenzenesulfonyl chloride **4** were known in the literature in 2005, and synthetic routes to both had been published as of 2005. It is not known, however, whether either compound was commercially available at the end of 2005. Nevertheless, with

the published routes a POSITA in 2005 would have been able to synthesize both 3-bromo-2-fluoroaniline **3** and 2,6-difluorobenzenesulfonyl chloride **4** by following the prior art without much experimentation. For example, 3-bromo-2-fluoroaniline **3** can be made by a procedure described in Acta Chem Scanda 29B, 981 (1975), whereby 2,3-dibromonitrobenzene is selectively displaced at the 2-position with potassium fluoride in dimethylformamide ("DMF"), to yield the corresponding fluorine-containing compound, which was then reduced in mediocre yield to 3-bromo-2-fluoroaniline **3**, with CuCl in acidic conditions. A number of other conditions suited for reducing a nitroaromatic compound to an aniline compound in the presence of bromine—such as using Fe/AcOH or hydrogenation using a poisoned palladium catalyst, as suggested in Scheme 2 of the '640 Patent—would also have been known to a POSITA in 2005. 2,3-Dibromonitrobenzene can itself be made in reasonable yield by nitration of 1,2-dibromobenzene.[25] The synthesis of 2,6-difluorobenzenesulfonyl chloride **4** from 2,6-difluorobenzenesulfonic acid, which I obtained commercially, involves a selective metalation between the two fluorine atoms, followed by a quench with sulfuryl chloride.[26]

42. To form *N*-(3-bromo-2-fluorophenyl)-2,6-difluorobenzenesulfonamide **5**, I combined 3-bromo-2-fluoroaniline **3** and 2,6-difluorobenzenesulfonyl chloride **4** with pyridine and 4-(N,N-dimethylamino)pyridine ("DMAP") in dichloromethane. The use of DMAP as a catalyst for acylation and silylation reactions was well known in the art in 2005, and the compound has also been used to catalyze sulfonation reactions.[27] DMAP is listed as a reagent in other parts of the specification of the '640 Patent, and a POSITA in 2005 would have understood that it could have been used to catalyze this reaction.

43. *N*-(3-bromo-2-fluorophenyl)-2,6-difluorobenzenesulfonamide **5** contains an aryl bromide, which enables its use in a Suzuki reaction whereby one can couple an aryl bromide containing both an acidic sulfonamide moiety in the bromine-containing ring and a fluorine atom next to the bromine atom in said ring. *N*-(3-bromo-2-fluorophenyl)-2,6-difluorobenzenesulfonamide **5** also contains one half of the biaryl unit of compound **2**, allowing us to use this reactant in both syntheses.

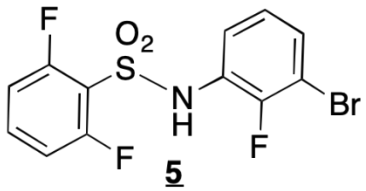
[25] *See, e.g.*, J. Org. Chem. 55, 2736 (1990).
[26] *See, e.g.*, J. Agric. Food Chem. 24, 1065 (1976).
[27] *See, e.g.*, J. Org. Chem. 57, 6234 (1992).

44. I then coupled *N*-(3-bromo-2-fluorophenyl)-2,6-difluorobenzenesulfonamide **5** with pyridine-4-boronic acid **6**, using conditions described as exemplary for Scheme 2 of the Asserted Patents. The use of 4-pinacolatopyridyl boronate to add 4-pyridyl units in an efficient manner to a highly hindered aromatic is described in Eur. J. Chem. 395 (2003), where four of the pyridyls were coupled simultaneously to a tetrabromo-[1.1.1.1]-metacyclophane with an overall 65% yield. The facile Suzuki couplings of pyridine-3-boronic acid with aromatic bromides and both electron-rich and electron-deficient heteroaromatic bromides to form 3-pyridyl biaryls is described in J. Med. Chem. 48, 224 (2005). A synthesis of pyridine-3-boronic acid, its dehydration to the cyclic trimer, and the use of that borate ester in Suzuki coupling to a heteroaromatic bromide is described in Org. Syn. 81, 89 (2005) and J. Org. Chem. 69, 2210 (2004). Pyridine-4-boronic acid **6** has been known since 1965, when it was first described in Rec. Trav. Chim. Pays-Bas 84, 430 (1965). A SciFinder search for such a reaction revealed that it had been included in almost 500 papers and patents by the end of 2005.

45. My synthesis of compound **1** was accomplished without excessive experimentation.

B. Detailed Experimental Section

1. Synthesis of Compound 5



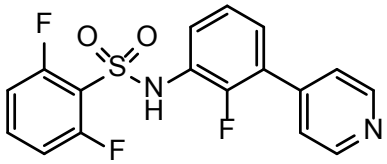
5

Compound 5: *N*-(3-bromo-2-fluorophenyl)-2,6-difluorobenzenesulfonamide

46. Below I describe in greater detail the steps undertaken to synthesize compound **1**. First, a solution of 3-bromo-2-fluoroaniline **3** (11.0 g, 57.9 mmol), 2,6-difluorobenzenesulfonyl chloride **4** (13.54 g, 63.6 mmol), pyridine (7. mL, 86.8 mmol), and 4-(*N,N*-dimethylamino)pyridine (1.16 mmol) in dichloromethane (250 mL) was stirred at 20º C. for 66 hrs. Aqueous hydrochloric acid (1M, 60 mL) was then added, the resultant mixture was stirred for 5 minutes, the layers were separated, and the aqueous layer was extracted with dichloromethane (100 mL). The combined organic phases were dried (Na_2SO_4), and the solvent was removed under reduced pressure. The crude material was purified on a Buchi Reveleris X2 chromatography system using a Redisep Rf silica gel column (330 g), eluting with 0-30%

ethyl/acetate hexanes at 100 mL/min. The product containing fractions were pooled, and the solvent was removed under reduced pressure to give *N*-(3-bromo-2-fluorophenyl)-2,6-difluorobenzenesulfonamide **5** (17.3 g, 82%) contaminated with about 10 mol% 3-bromo-2-fluoroaniline, as an off-white solid. The structure of compound **5** was confirmed by nuclear magnetic resonance ("NMR") spectroscopy and by mass spectrometry ("MS"): (1) ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 6.95 (1H, dt, J d = 1.6 Hz, Jt = 8.2 Hz, aniline H5), 6.99 2H, sl br t, J = 8.6 Hz, H3 &H5 phenylsulfonyl), 7.26 (1H, ddd, J = 8.2, 6.4, 1.6 Hz, aniline H4), 7.31 (1H, brs, NH), 7.50 (1H, tt, J = 8.5, 6.0 Hz, phenylsulfonyl H4), 7.56 (1H, ddd, J = 8.4, 7.1, 1.4 Hz, aniline H6); (2) ^{13}C NMR (100 MHz $CDCl_3$), δ: 109.07 (d, J = 19.8 Hz, C2 aniline), 113.18 (dd, J = 22.7, 3.7 Hz, phenylsulfonyl C3 & C5), 116.55 (s, C1 phenylsulfonyl), 121.13 (s, C6 aniline), 125.14 (d, J = 13.2 Hz, C1 aniline), 125.51 (d, J = 5.2 Hz, aniline C4), 129.77 (s, C5 aniline), 135.48 (t, J = 11 Hz, phenylsulfonyl C4), 150.33(d, J =244.3 Hz, aniline C3), 159.68 (dd, J = 259.7, 3.6 Hz, phenylsulfonyl C2 & C6); (3) ^{19}F-NMR (376 MHz, $CDCl_3$) δ -106.87 (2F, very narrow m), -123.08 (1F, very narrow m); (4) MS m/z 365.1 (100, MH^+), 366.1 (21, $^{13}CMH^+$); (5) MS m/z 365.9 (99, $^{79}BrMH^+$), 367.9 (100, $^{81}BrMH^+$).

2. Synthesis of Compound 1



1

Compound 1: *N*-(2-Fluoro-3-(pyrid-4-yl)phenyl)-2,6-difluorobenzenesulfonamide

47. Aqueous potassium carbonate solution (2M, 3.0 mL, 6 mmol) was then added to a mixture of *N*-(3-bromo-2-fluorophenyl)-2,6-difluorobenzenesulfonamide **5** (1.10 g, 3.0 mmol) and pyridine-4-boronic acid (0.55 g, 4.5 mmol) in acetonitrile (15 mL) at 20º C., and the mixture was sparged with nitrogen for 10 minutes. Tetrakis(triphenylphosphine)palladium (0.35 g, 0.3 mmol) was then added, and the resultant mixture was refluxed for 16 hours under nitrogen. LCMS analysis showed the reaction was complete, and after cooling to 20º C., the reaction mixture was diluted with ethyl acetate (200 mL) and rinsed with water (40 mL) and saturated brine (40 mL). The combined aqueous washes were back-extracted with ethyl acetate (100 mL), and the combined organic phases were dried (Na_2SO_4). The

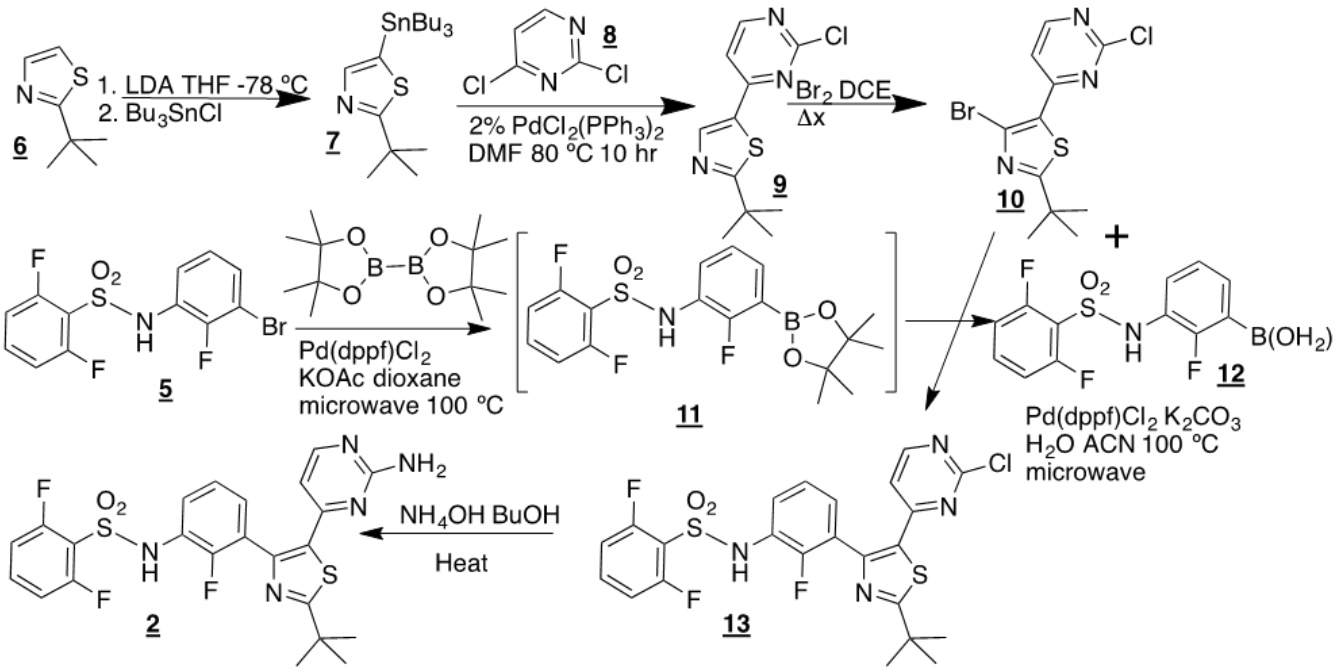
solvent was removed under reduced pressure, and the residue was purified by flash chromatography (Buchi Reveleris X2 chromatography system using a Redisep Rf silica gel column (60 g) eluting with 0-5% methanol/dichloromethane). The product containing fractions were then pooled, and the solvent was removed under reduced pressure to give a white solid (1.0 g), which was triturated with toluene (10 mL), and the solid collected and dried to give *N*-(2-fluoro-3-(pyrid-4-yl)phenyl) 2,6-difluorobenzenesulfonamide **1** (0.69 g, 63%) as a white solid. The structure of compound **1** was confirmed by NMR spectroscopy and by MS: (1) ^{1}H NMR (400 MHz $CDCl_3$) δ: 7.26-7.33 (3H, m, aniline H4, phenylsulfonyl H3 & H5), 7.38-7.48 (4H, m, pyridyl H3& H5, aniline H5 & H6), 7.72 (1H, tt, J = 8.5, 6.1 Hz, phenylsulfonyl H4), 8.65 (1H, dd, J = 4.5, 1.6 Hz), pyridyl H2 & H6), 10.94 (1H, brs, NH); (2) ^{13}C NMR (100 MHz $CDCl_3$) δ: 113.77 (dd, J = 23.1, 3.3 Hz, phenylsulfonyl C3 & C5), 117.98 (t, J = 16.1 Hz, phenylsulfonyl C1), 123.77 (d, J = 3.6 Hz, aniline C4), 125.00 (d, J = 13.2 Hz, aniline C1/3), 125.59 (d, J = 4.4 Hz, aniline C4), 126.89 (d, J = 11.7 Hz, aniline C3/1), 128.12 (pyridyl C3), 128.73 (d, J = 1.5 Hz, aniline C5), 136.41 (t, J = 11.4 Hz, phenylsulfonyl C4), 142.32 (pyridyl C4), 150.48 (pyridyl C2 & C5), 153.42 (d, J = 251.6 Hz, aniline C2), 159.23 (dd, J = 257.5, 3.7 Hz, phenylsulfonyl C1); (3) ^{19}F NMR (376 MHz ($(CD_3)_2SO$) δ: -128.40 (1F, aniline), 107.33-107.38 (2F, complex sextet, J_{app} 5.4, 4.1, 2.7 Hz); (4) MS m/z 365.1 (100, MH^+), 366.1 (21, $^{13}CMH^+$).

VIII. SYNTHESIS OF COMPOUND 2

48. At my direction, scientists at Adesis, Inc. also synthesized *N*-[3-[5-(2-aminopyrimidin-4-yl)-2-(1,1-dimethylethyl)-4-thiazolyl]-2-fluorophenyl]-2,6-difluorobenzenesulfonamide, which I understand to be the IUPAC name for the drug dabrafenib. Except where expressly noted otherwise, all reagents used in the synthesis were commercially available in 2005, and were obtained from the sources set forth in Appendix A.

A. Synthetic Scheme for Compound 2

49. An overview of the synthetic scheme I followed to synthesize compound **2** is below, with reactants and intermediaries referred to by compound number:



50. There were a number of potential routes one could have chosen to prepare compound **2**, using a Suzuki coupling to form the biaryl bond between the sulfonated aniline and the thiazole 4-position. These include how one chooses to activate the 4- and 5-positions of the thiazole, where even if one limits oneself to simple metalations or brominations of a 2-t-butyl thiazole (or its keto-precursor), there are multiple options going forward. I elected to start with 2-t-butylthiazole **6** rather than, for example, its 4-oxo or 4,5-dioxo precursors, which could be readily turned into the corresponding 4- or 4,5-dibromothiazoles, where elaboration routes remarkably similar to that chosen could be carried out.

51. 2-t-Butylthiazole **6** was known in the scientific literature before 2006,[28] and I purchased it as the starting material. I also made 2-t-Butylthiazole **6** from commercially available materials, performing a simple modification of the synthesis described in the Comptes Rendus reference. This involved converting 2,2,-dimethylpropanamide into the corresponding thioamide, 2,2,-dimethylpropanthionamide, with Lawesson's Reagent.[29] Treatment of this thionamide with the diethylacetal of bromoacetaldehyde under acidic conditions alkylates the thionamide, and then condenses

[28] *See* Comptes Rendus 252, 1619 (1961); *see also* Bull Soc Chim France 1794 (1962).
[29] *See, e.g.*, Tetrahedron 41, 5061 (1985).

the acid-liberated aldehyde with the amine portion of the thionamide to give the desired 2-t-Butylthiazole **6**.

52. To synthesize 2-(1,1-dimethylethyl)-5-(tributylstannyl)thiazole **7**, I began by lithiating 2-t-butylthiazole **6**. The lithiation of 2-substituted thiazoles on the 5-position is well precedented,[30] with the 5-position hydrogen probably being around 10 pKa units more acidic than the 4-position hydrogen. This was followed by quenching the 5-lithiothiazole with a stannyl chloride to yield the corresponding 5-stannylthiazole. When I carried out this protocol on 2-t-butylthiazole **6**, I obtained the desired 2-(1,1-dimethylethyl)-5-(tributylstannyl)thiazole **7** in 65% yield on a multigram scale.

53. The coupling of 5-stannylthiazoles with heteroaryl bromides to give 5-heteroarylthiazoles is precedented.[31] To synthesize 5-(2-chloropyrimidin-4-yl)-2-(1,1-dimethylethyl)thiazole **9**, I performed a selective Stille coupling of 2-(1,1-dimethylethyl)-5-(tributylstannyl)thiazole **7** with 2,4-dichloropyrimidine **8**. The selective Stille coupling of arylstannanes such as 5-(2-chloropyrimidin-4-yl)-2-(1,1-dimethylethyl)thiazole **9** with only the 4-chlorine in 2,4-dichloropyrimidine **8** to give 2-chloro-4-arylpyrimidines was well known by 2005.[32] The displacement of 2-chloropyrimidines with amines under mild conditions has been known in the art for more than 50 years, suggesting the introduction of the amine in the last step would be straightforward.[33] A POSITA in 2005 would have known that a different coupling reagent such as 2-amino-4-chloropyridine could also have been selected to perform the Stille coupling, as such couplings were well established by that time.[34] As I suspected, the Stille coupling proved to be straightforward, and 2-(1,1-dimethylethyl)-5-(tributylstannyl)thiazole **7** was converted into 5-(2-chloropyrimidin-4-yl)-2-(1,1-dimethylethyl)thiazole **9** with 58% yield.

54. I then brominated the 4-position of 5-(2-chloropyrimidin-4-yl)-2-(1,1-dimethylethyl)thiazole **9** to obtain 4-bromo-5-(2-chloropyrimidin-4-yl)-2-(1,1-dimethylethyl)thiazole **10**, a key intermediate for any Suzuki-coupling synthesis of compound **2**. 4-Bromination of 2,5-disubstituted

[30] *See* Synthesis (1986) 757; *see also* Tetrahedron Letters 43, 8845 (2002).
[31] *See* Synthesis (1987) 185; *see also* Bioorg Med Chem 12, 5579 (2004).
[32] *See* Acta Chemica Scanda 43, 62 (1989); *see also* in SynLett (2000) 829.
[33] *See, e.g.*, Organic Syntheses 35, 58 (1955) (discussing displacements with methylamine and dimethylamine).
[34] *See, e.g.*, WO 2001/000213; US 5863924.

thiazoles similar to 5-(2-chloropyrimidin-4-yl)-2-(1,1-dimethylethyl)thiazole **9** was known by 2005. For example, the bromination of 5-methyl-2-(pyrid-2-yl)thiazole with bromine in acetonitrile/chloroform is described in New J Chem 29, 439 (2005), and a number of 4-brominations of 2,5-disubstituted thiazoles are described in WO 2005/116000. Although the conditions described in some of the literature proved to be impractically slow, simple refluxing of 5-(2-chloropyrimidin-4-yl)-2-(1,1-dimethylethyl)thiazole **9** in a large excess of liquid bromine as the solvent, a process known to persons of ordinary skill in the art as of 2005,[35] resulted in a slow bromination and 56% overall yield.

55. The other arm of the synthesis involved taking the already formed *N*-(3-bromo-2-fluorophenyl)-2,6-difluorobenzenesulfonamide **5** from the synthesis of compound **1** and borylating it. I reacted *N*-(3-bromo-2-fluorophenyl)-2,6-difluorobenzenesulfonamide **5** with bis-(pinacolato)diborane with microwave heating, a well-established technique for borylations by 2005.[36] This led to about 50% boronylation, but resulted in the desterified product 3-(2,6-difluorophenylsulfonamido)-2-fluorophenyl boronoic acid **12**, rather than its expected pinacolyl ester **11**. As the boronic acid **12** is closer to the original Scheme 2 reaction than is the ester **11**, I did not investigate this reaction further, but simply took the crude boronic acid **12** (~50% pure) and then used it in the Suzuki coupling reaction without any purification.

56. 4-bromo-5-(2-chloropyrimidin-4-yl)-2-(1,1-dimethylethyl)thiazole **10**, a bromide, and 3-(2,6-difluorophenylsulfonamido)-2-fluorophenyl boronic acid **12**, a boronic acid, were then subjected to a Suzuki coupling under conditions nearly identical to those described in Scheme 2 of the Asserted Patents, with the only major difference being the use of the superior catalyst $PdCl_2$(dppf) dichloromethane. This reaction worked the first time it was tried, forming the concatenated triaryl **13**. The reaction was run in a sealed tube in a microwave, as suggested in Scheme 2 of the Asserted Patents, as well as other references.[37] The reaction was then repeated on twice the scale, and the two reaction

[35] *See* Chem Berichte 126, 1643 (1993); *see also* Tetrahedron Letters 12, 1583 (1971); *ibid.* at 15, 115 (1974); Z. Anorg Alig Chemie 623, 623 (1997).

[36] *See, e.g.*, SynLett 1204 (2003). For use of bis-pinacolatodiboron and Pd(dppf)Cl_2, *see* J. Org. Chem. 60, 7508 (1995), *ibid.* 65, 164 (2000). For use on N-(3-bromo)sulfonamides, *see* WO 2004/052847.

[37] *See, e.g.*, Angew Chem Int Edn 43, 6250 (2004); Organic Letters 6, 1473 (2004); J. Org. Chem. 69, 4821 (2004).

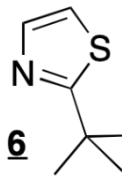
mixtures were combined together and purified to give the Suzuki coupled product **13** in 82% purity and 42% uncorrected yield. Chloride **13** was then heated to 100º C. with ammonium hydroxide in n-butanol which displaced the ammonia, and gave compound **2** in about 30% yield after purification, completing the synthesis in 8 steps overall from commercially available starting materials. If each of the starting materials had to be made from common laboratory compounds, this would add another 6 steps in total to this process.

57. It is important to emphasize at this juncture that although I chose this particular synthetic route, I could have chosen many variants on this route to attempt, all of them with literature precedent for a 2005 POSITA. I have not explored any of the variants, or done any work to validate them, but there is no reason to believe *a priori* that several of them would not have worked equally well or perhaps even better than the route I chose to follow.

58. My synthesis of compound **2** was accomplished without excessive experimentation.

B. Detailed Experimental Section

1. Synthesis of Compound 6



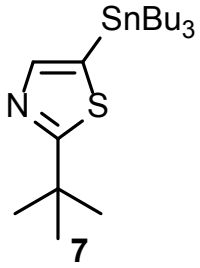
6

Compound 6: 2-t-Butylthiazole

59. Our synthesis of 2-t-butylthiazole **6** began with a mixture of 2,2-dimethylpropanamide (17.56 g, 173.6 mmol) and Lawesson's reagent (70.2 g, 173. 6 mmol) in THF (400 mL), which was refluxed under nitrogen for 7 hours and then stirred at 20º C. for 16 hours. The reaction mixture was concentrated under reduced pressure, and the residue was purified in two batches on a Buchi Reveleris X2 chromatography system using a Redisep Rf silica gel column (330 g), eluting with 0-40% ethyl/acetate heptanes at 100 mL/min. The product containing fractions were pooled and the solvent was removed under reduced pressure to give 2,2-dimethylpropanthionamide (12.7 g, 62%) as an off white, slightly sticky solid.

60. A solution of 2,2-dimethylpropanthionamide (10.2 g, 87.2 mmol) and 2-bromo-1,1,diethoxyethane (17.05 mL, 113.3 mmol) was then refluxed in ethanol (200 mL) containing dilute hydrochloric acid (3M, 20 mL) for 16 hours. Upon cooling, the solution was concentrated under reduced pressure, poured onto ethyl acetate (500 mL), and rinsed with saturated aqueous sodium bicarbonate solution (300 mL). The aqueous phase was extracted with ethyl acetate (2 x 100 mL), and the combined organic phases were washed with saturated brine (200 mL), and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue was purified on a Buchi Reveleris X2 chromatography system using a Redisep Rf silica gel column (330 g), eluting with 0-20% ethyl/acetate heptanes at 100 mL/min. The solvent was removed under reduced pressure to give 2-t-butylthiazole **6** (2.8 g, 23%) as a rather volatile pale yellow oil. The structure of compound **6** was confirmed by NMR spectroscopy: (1) ^{1}H NMR (400 MHz $CDCl_3$) δ: 1.41 (9H, s, t-Bu), 7.13 (1H, d, J = 3.4 Hz, H5), 7.63 (1H, d, J = 3.3 Hz, H4); and (2) ^{13}C NMR (100 MHz $CDCl_3$) δ: 30.85 (Me), 37.38 (quaternary), 117.35 (C5), 141.85 (C4), 181.19 (C2).

2. Synthesis of Compound 7



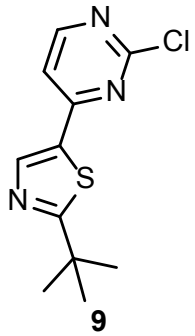
7

Compound 7: 2-(1,1-Dimethylethyl)-5-tributylstannyl)thiazole

61. Next, n-butyl lithium (2.5 M in hexanes, 33.0 mL, 82.4 mmol) was added dropwise to a solution of diisopropylamine (14.44 mL, 103 mmol) in anhydrous tetrahydrofuran ("THF") (70 mL) stirred under nitrogen at 0º C. After 30 minutes, the reaction mixture was cooled to -78º C., and a solution of 2-t-butylthiazole **6** (9.70 g, 68.7 mmol) in THF (10 mL) was added dropwise, and the reaction mixture was stirred at -78º C. for a further hour. Tri-n-butyltin chloride (22.36 mL, 82.4 mmol) was added dropwise, and then the reaction mixture was allowed to warm up slowly to 20º C. over 3 hours, when LCMS analysis showed the reaction was complete. The reaction mixture was quenched by adding saturated aqueous ammonium chloride solution (50 mL), and the mixture was extracted with ether (200

mL, 2 x 100 mL). The combined extracts were washed with saturated brine (50 mL), dried (Na_2SO_4), and the volatiles were removed under reduced pressure to give the crude product as a brown oil (40 g). The crude material was purified on a Buchi Reveleris X2 chromatography system using a Redisep Rf silica gel column (330 g) eluting with 0-20% ethyl/acetate heptanes at 100 mL/min. The product containing fractions were pooled and the solvent was removed under reduced pressure to give 2-(1,1-dimethylethyl)-5-(tributylstannyl)thiazole **7** (19.27 g, 65%) as a pale yellow oil. The structure of compound **7** was confirmed by NMR spectroscopy and MS: (1) ^{1}H NMR (400 MHz $CDCl_3$) δ: 0.89 (9H, t, J = 7.4 Hz, Mes), 1.08-1.12 (6H, m $SnCH_2$), 1.30-1.36 (6H, m, CH_2Me), 1.46 (9H, s, t-butyl), 1.51-1.60 (6H, m, $SnCH_2CH_2$), 7.60 (1H, s, H4); (2) ^{13}C NMR (100 MHz $CDCl_3$) δ: 10.84 (SnC), 13.58 (CH_2Me), 27.16 (CH_2Me), 28.88 ($SnCCH_2$), 31.08 (t-butyl Me), 37.44 (quaternary), 126.31 (thiazole C5), 148.51 (thiazole C4), 186.21 (thiazole C2); (3) MS m/z 428.1 (37, $^{116}SnMH^+$), 429.2 (31, $^{117}SnMH^+$), 430.2 (73, $^{118}SnMH^+$), 432.2 (100, $^{120}SnMH^+$), 433.2 (22, $^{120}Sn^{13}CMH^+$), 436.2 (17, $^{124}SnMH^+$).

3. Synthesis of Compound 9



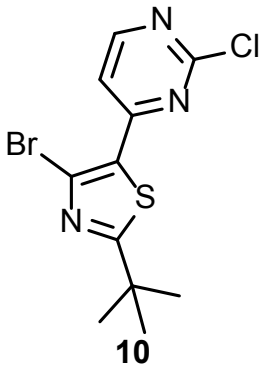
9

Compound 9: 5-(2-Chloropyrimidin-4-yl)-2-(1,1-dimethylethyl)thiazole

62. A solution of 2-(1,1-dimethylethyl)-5-(tributylstannyl)thiazole **7** (18.21 g, 42.3 mmol) and 2,4-dichloropyrimidine **8** (5.73 g, 38.47 mmol) in DMF (270 mL) was sparged with nitrogen for 10 minutes. Bis-(triphenylphosphine)palladium dichloride (1.35 g, 1.92 mmol) was added, and the mixture was further sparged with nitrogen for 5 minutes. The reaction mixture was then stirred on a 90º C. oil bath for 16 hours, when LCMS analysis showed that the reaction was complete. The mixture was concentrated under reduced pressure, and the residual mixture was poured onto water (100 mL) and extracted with ethyl acetate (200 mL), and the organic extracts were washed with saturated brine (50

mL). The combined aqueous phases were back extracted with further ethyl acetate (3 x 100 mL) and the combined organic phases were dried (Na_2SO_4). The crude material was purified on a Buchi Reveleris X2 chromatography system using a Redisep Rf silica gel column (330 g), eluting with 0-50% ethyl/acetate heptanes at 100 mL/min. The product containing fractions were pooled and the solvent was removed under reduced pressure to give 5-(2-chloropyrimidin-4-yl)-2-(1,1-dimethylethyl)thiazole **9** (7.78 g, 80%) as a pale yellow solid. The structure of compound **9** was confirmed by NMR spectroscopy and MS: (1) ^{1}H NMR (400 MHz $CDCl_3$) δ: 1.48 (9H, s, t-butyl), 7.47 (1H, d, J = 5.3 Hz, pyrimidyl H5), 8.31 (1H, s thiazole H4), 8.56 (1H, d, J = 5.3 Hz, pyrimidyl H6); (2) ^{13}C NMR (100 MHz $CDCl_3$) δ: 30.66 (Me), 38.33 (quaternary C), 114.12 (pyrimidyl C5), 134.77 (thiazole C5), 143.55 (thiazole C4), 159.48 (pyrimidyl C2), 160.70 (pyrimidyl C6), 161.74 (pyrimidyl C4), 186.94 (thiazole C2); (3) MS m/z 254.1 (100, $^{35}ClMH^+$), 255.1 (15, $^{13}C^{35}ClMH^+$), 256.0 (38, $^{37}ClMH^+$), 257.0 (10, $^{13}C\,^{37}ClMH^+$).

4. Synthesis of Compound 10



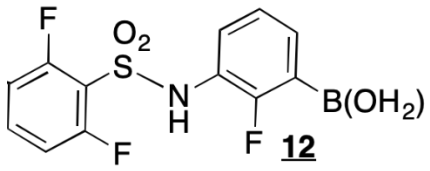
10

Compound 10: 4-Bromo-5-(2-chloropyrimidin-4-yl)-2-(1,1-dimethylethyl)thiazole

63. 5-(2-Chloropyrimidin-4-yl)-2-(1,1-dimethylethyl)thiazole **9** (3.83 g, 15.1 mmol) was heated at 60° C. in bromine (23.3 mL, 453 mmol) for 8 hours, and was then stirred at 20° C. for 16 hours. The reaction mixture was diluted with ethyl acetate (200 mL), and the organic phase was washed with saturated aqueous sodium bicarbonate solution (200 mL) and saturated brine (100 mL). The aqueous phases were back-extracted with ethyl acetate (2 x 100 mL) and the combined organic phases were dried (Na_2SO_4). The crude material was purified on a Buchi Reveleris X2 chromatography system using a Sorbtech silica gel column (120 g) eluting with 0-50% ethyl/acetate heptanes at 60 mL/min. The product containing fractions were pooled and the solvent was removed under reduced pressure to give 4-bromo-5-(2-chloropyrimidin-4-yl)-2-(1,1-dimethylethyl)thiazole **10** (2.56 g, 56%) as an off-white solid. The

structure of compound **10** was confirmed by NMR spectroscopy and MS: (1) ^{1}H NMR (400 MHz $CDCl_3$) δ: 1.47 (9H, s, methyls), 8.30 (1H, d, J = 5.4 Hz, pyrimidyl H5), 8.66 (1H, d, J = 5.4 Hz, pyrimidyl H6); (2) ^{13}C NMR (100 MHz $CDCl_3$) δ: 30.31, Me), 38.42, (3^{ry} C), 114.51 (pyrimidyl C5), 125.97 (thiazole C4), 129.89 (thiazole C5), 159.62 (pyrimidyl C2), 159.96 (pyrimidyl C6), 161.16 (pyrimidyl C4), 185.57 (thiazole C2); (3) MS m/z 331.9 ($^{79}Br^{35}ClMH^+$), 333.9 (100%, $^{81}Br^{35}ClMH^+$ & $^{79}Br^{37}ClMH^+$, 335.9 ($^{81}Br^{37}ClMH^+$).

5. Synthesis of Compound 12

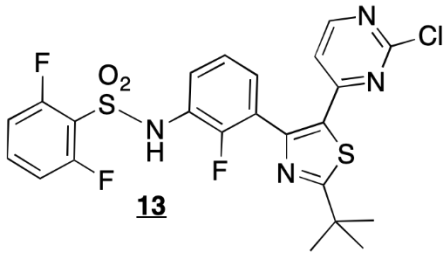


12

Compound 12: 3-(2,6-Difluorobenzenenesulfonamido)-2-fluorophenyl boronic acid

64. A mixture of N-(3-bromo-2-fluorophenyl) 2,6-difluorobenzenesulfonamide **5** (734 mg, 2.0 mmol), 4,4,4′,4′,5,5,5′,5′-octamethyl-2,2′-bi-1,3,2-dioxaborolane (609 mg, 2.4 mmol), potassium acetate (393 mg, 4 mmol), and [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (146 mg, 0.2 mmol) in dioxane (15 mL) was sparged with nitrogen for 5 minutes, and then heated at 100º C. in a sealed tube in a microwave reactor for 1 hour. LCMS analysis showed that the reaction had occurred, and that the product was the boronic acid **12**, not the expected pinacol boronic ester **11**. The reaction mixture was filtered through celite (30 g), rinsed with ethyl acetate (2 x 50 mL), and the combined filtrates were evaporated under reduced pressure to give crude 3-(2,6-difluorobenzenenesulfonamido)-2-fluorophenyl boronic acid **12** (~50% pure according to LCMS analysis), which was used directly in the subsequent reaction.

6. Synthesis of Compound 13

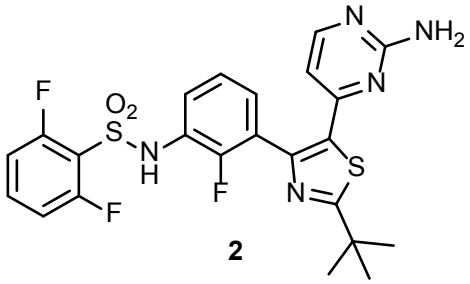


13

Compound 13: *N*-[3-[5-(2-Chloropyrimidin-4-yl)-2-(1,1-dimethylethyl)-4-thiazolyl]-2-fluorophenyl]-2,6-difluorobenzenesulfonamide

65. Crude 3-(2,6-difluorobenzenenesulfonamido)-2-fluorophenyl boronic acid **12** from the previous reaction (~1 mmol), 4-bromo-5-(2-chloropyrimidin-4-yl)-2-(1,1-dimethylethyl)thiazole **10** (166 mg, 0.5 mmol), and [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) dichloromethane complex (82 mg, 0.1 mmol) in dioxane (15 mL) containing aqueous potassium carbonate solution (2M, 0.75 mL) was sparged with nitrogen for 5 minutes, and was then heated at 80° C. for 2 hours, when LCMS analysis showed the product was formed. This reaction was then repeated on twice the scale, and the combined reaction mixtures were diluted with ethyl acetate (200 mL) and washed with water (20 mL) and saturated brine (20 mL). The combined aqueous washes were back-extracted with ethyl acetate (2x 50 mL), and the combined organic phases were dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue was purified on a Buchi Reveleris X2 chromatography system using a Sorbtech silica gel column (40 g), eluting with 0-40% ethyl/acetate heptanes at 40 mL/minute. The product containing fractions were pooled and the solvent was removed under reduced pressure to give impure N-[3-[5-(2-chloropyrimidin-4-yl)-2-(1,1-dimethylethyl)-4-thiazolyl]-2-fluorophenyl]-2,6-difluorobenzenesulfonamide **13** (340 mg, ~42% based on bromide) as brown oil. The structure of compound **13** was confirmed by mass spectrometry: MS m/z 539 (100, $^{35}ClMH^+$), 540 (28, $^{35}Cl^{13}CMH^+$), 541 (42, $^{37}ClMH^+$), 542 (11, $^{37}Cl^{13}CMH^+$).

7. Synthesis of Compound 2



2

Compound 2: *N*-[3-[5-(2-aminopyrimidin-4-yl)-2-(1,1-dimethylethyl)-4-thiazolyl]-2-fluorophenyl]-2,6-difluorobenzenesulfonamide

66. Finally, a suspension of impure N-[3-[5-(2-chloropyrimidin-4-yl)-2-(1,1-dimethylethyl)-4-thiazolyl]-2-fluorophenyl]-2,6-difluorobenzenesulfonamide **13** (300 mg, ~0.56 mmol) in n-butanol (20 mL) containing saturated aqueous ammonia (20 mL) was heated in a sealed tube at 100º C. for 4 hours, when LCMS analysis showed product was formed. This reaction mixture was combined with a pilot

scale reaction (using 32 mg of N-[3-[5-(2-chloropyrimidin-4-yl)-2-(1,1-dimethylethyl)-4-thiazolyl]-2-fluorophenyl]-2,6-difluorobenzenesulfonamide **13**), and the reaction mixtures were diluted with ethyl acetate (200 mL), rinsed with water (20 mL) and saturated brine (20 mL), and then dried (Na_2SO_4). The solvent was then removed under reduced pressure, and the residue was purified on a Buchi Reveleris X2 chromatography system using a Sorbtech silica gel column (25 g), eluting with 0-100% ethyl/acetate heptanes at 28 mL/minute. The product containing fractions were pooled and the solvent was removed under reduced pressure to give N-[3-[5-(2-aminopyrimidin-4-yl)-2-(1,1-dimethylethyl)-4-thiazolyl]-2-fluorophenyl]-2,6-difluorobenzenesulfonamide **2** (94 mg, 12% on two steps) as a yellow foam, containing about 1 equivalent of ethyl acetate. The structure of compound **2** was confirmed by NMR spectroscopy and mass spectrometry: (1) ^{1}H NMR (400 MHz $CDCl_3$) δ: 1.45 (9H, s *t*-Bu), 5.30 (2H, brs, NH_2), 6.14 (1H, d, J = 5.2 Hz, pyrimidyl H5), 6.94 (2H, t, J = 8.8 Hz, phenylsulfonyl H3 & 5), 7.21 (1H, t, J = 7.9 Hz) aniline H5), 7.37 (ddd J = 7.9, 6.4, 1.5 Hz aniline H4/6), 4.41-7.47 (1H, m, aniline H6/4), 7.70 (dt, Jd = 1.6 Hz, Jt = 8.4 Hz, phenylsulfonyl H4), 7.88 (1H, d, J = 5.2 Hz, pyrimidyl H6); (2) ^{13}C NMR (100 MHz $CDCl_3$) δ: 30.70 (Me), 38.03 (3^{ry} C), 107.30 (pyrimidyl C5), 113.12 (dd, J = 23.5, 3.7 Hz, phenylsulfonyl C3 & C5), 117.25 (t, J = 15.4 Hz, phenylsulfonyl C1), 124.30 (t, J = 15.3 Hz, phenylsulfonyl C1), 124.59 (aniline C54), 125.10 (d, J = 4.4 Hz, aniline C6), 127.38 (aniline C3), 128.59 (aniline C5), 133.70 (thiazole C5), 135.09 (t, J = 11.0 Hz, phenylsulfonyl C4), 145.82 (pyrimidyl C4), 151.61 (d, J = 248.7 Hz, aniline C2), 158.05 (thiazole C4), 159.31 (pyrimidyl C6) 159.74 (dd, J = 259.7, 3.7 Hz, phenylsulfonyl C2 & C6), 162.66 (pyrimidinyl C2), 182.97 (thiazole C2); (3) ^{19}F NMR (376 MHz $CDCl_3$) δ: -128.60 (1F, aniline), 106.79 (2F, complex pentet, J_{app} 5.5, 4.1 Hz); (4) MS m/z 520.1 (100, MH^+) 521.1 (26, $^{13}CMH^+$). The ^{1}H NMR was retaken after spiking it with an authentic commercial sample of dabrafenib. No new peaks were seen.

Date: 3/14/19

Alexander J. Bridges

Dr. Alexander J. Bridges

Appendix A – Commercial Sources of Starting Materials

3-Bromo-2-fluoroaniline	CombiBlocks
2,6-Difluorobenzenesulfonic acid	CombiBlocks
Triethylamine	Oakwood
Pyridine	Sigma Aldrich
4-DMAP	Sigma Aldrich
Pyridine-4-boronic acid	CombiBlocks
Pd (PPh3)4.	Oakwood
n-Butyl lithium	Sigma Aldrich
Diisopropylamine	Sigma Aldrich
2-t-Butylthiazole	Enamine
Tributyltin chloride	Sigma Aldrich
2,4-Dichloropyrimidine	CombiBlocks
PdCl2(PPh3)2	Johnson Matthey
Bromine	Sigma Aldrich
Bis(pinacolato)diboron	CombiBlocks
PdCl2(dppf)	Johnson Matthey
PdCl2(dppf).DCM	Johnson Matthey
NH4OH	Sigma Aldrich
Trimethylacetamide	Sigma Aldrich
Lawessons Reagent	Sigma Aldrich
Bromoacetaldehyde diethyl acetal	Sigma Aldrich

PROOF OF SERVICE

I am employed in San Francisco County, State of California, in the office of a member of the bar of this Court, at whose direction the service was made. I am over the age of eighteen years, and not a party to the within action. My business address is 217 Leidesdorff Street, San Francisco, CA 94111.

On March 14, 2019, I served the following documents in the manner described below:

REBUTTAL EXPERT REPORT OF DR. ALEXANDER J. BRIDGES

[X] BY ELECTRONIC SERVICE: By electronically mailing a true and correct copy through Durie Tangri's electronic mail system from cortega@durietangri.com to the email addresses set forth below.

On the following part(ies) in this action:

Thomas P. Steindler
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Telephone: 202-756-8000
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William G. Gaede, III
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Attorneys for Defendant
Novartis Pharmaceuticals Corporation

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct. Executed on March 14, 2019, at San Francisco, California.

Christina Ortega

EXHIBIT 1

ALEXANDER JAMES BRIDGES

CURRICULUM VITAE

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Saline, MI 48176

Telephone: h 734 316 7104
c 734 904 0296

Citizenship: British/USA

EDUCATION

Oxford University

B.A. in Chemistry, First Class Honours, 1972
Thesis (with Dr. Jeremy R. Knowles): "The Use of Photogenerated Reagents in Protein Chemistry"

D. Phil., 1974
Thesis (with Dr. Gordon H. Whitham): "Synthetic and Mechanistic Studies in Alicyclic Chemistry"

POST-DOCTORAL EXPERIENCE

October 1974-October 1976 NATO Fellowship at The University of Wisconsin at Madison, with Prof. Barry M. Trost

November 1976-July 1977 Temporary Charge de Recherche at the CNRS Gif-sur-Yvette, with Prof. P. Potier

August 1977-August 1978 Research Associate at The University of Toronto, with Prof. J. B. Jones

EMPLOYMENT HISTORY

January 2016-present BioMarin Pharmaceuticals Inc.
San Rafael CA 94949

This is about a 25% appointment. I have been an occasional consultant to BioMarin since 2010. BioMarin is developing small molecule therapeutics for genetic orphan diseases, and I consult on these programs.

May 2014-December 2016 Oncofusion Therapeutics Inc.
Ann Arbor, MI 48105

Chemistry Consultant. This was a 20% appointment in a start-up company being spun out of the University of Michigan, by the founders of Ascenta Therapeutics Inc. The company aimed to commercialize compounds developed in Professor Shaomeng Wang's laboratories against a wide variety of oncology targets.

April 2011-November 2012 JBR Pharma Inc.
Ann Arbor, MI 48105

Chief Scientific Officer. This was a half time position in a start-up company being spun out of the University of Michigan to develop Rho kinase (ROCK) inhibitors from the laboratory of Professor Gary Glick. The company was virtual, and my role was to improve the profile of the compounds licensed in, in order that the company would be attractive enough to acquire. This involved supervision of synthetic chemists in China, and getting appropriate biology testing done to improve the potency of the compounds. The acquisition was finalized in January 2013.

July 2008-present Full-Time Consultant

Whilst working at Quatrx, I was a part time consultant in Medicinal Chemistry for several companies. At the end of July 2008, I left Quatrx, as my skill set was no longer relevant to Quatrx's new focus as a Phase II/III development company. Since then I have been a full-time consultant for several pharmaceutical companies, specializing in synthetic chemistry, including some process chemistry, medicinal chemistry and due diligence evaluation of preclinical packages. This included recommendations to acquire the proteasome inhibitor Carfilzomib, when I was the main chemistry consultant for Onyx Pharmaceuticals, and the recommendation to BioMarin Pharmaceuticals to acquire the PARP inhibitor Talazoparib. I am affiliated with a pharmaceutical consulting firm, IDSC, based in Chelsea, Michigan, which is largely staffed by ex-Pfizer colleagues. Overall, I have consulted for over twenty companies, and half a dozen universities.

July 2003-July 2008 Quatrx Pharmaceuticals Inc
777 E. Eisenhower Parkway, Suite 100
Ann Arbor, MI 48108

Senior Director of Preclinical Sciences. May 2007-July 2008. *Director of Preclinical Sciences*. July 2003-May 2007. Quatrx licenses in drugs for clinical development preferably pre-IND, and has an emphasis on early clinical trials, prior to outlicensing compounds. Quatrx is a virtual company, and does almost all of its work via CROs. My responsibilities included the initial evaluation of all of the preclinical packages for potential licensing opportunities, including chemotype, chemistry, manufacturability, pharmacology, pharmacokinetics and preliminary patentability determination, which included Osphena, which has a recently granted NDA. Once Quatrx had licensed in a compound, I was responsible for making sure that the pharmacology and PK packages were complete for an IND, and were ready to be put into the IND. I was also responsible for ensuring that a GMP synthesis was established, and that the API was in a useable form, and that the CMC section of the IND was complete. I designed pharmacology and PK studies, selected a salt for one API, and did the bench chemistry to design a feasible and patentable route to a Vitamin D API, becocalcidiol, and to make novel, patentable, pro-drugs of a third.

June 2000-June 2003 Pfizer Global Research and Development
Ann Arbor Laboratories
2800 Plymouth Road
Ann Arbor, MI 48105

Oncology Discovery Executive Director. November 2001-June 2003. I was appointed to the site head position on a full-time basis in November 2001. I retained responsibility for Oncology chemistry on site, and I had overall responsibility for all oncology discovery science on site, until the Pfizer takeover of Pharmacia led to the discontinuation of Oncology at the Ann Arbor site. During that time, I was a member of the senior discovery management team on site, and a member of the worldwide Discovery Management Committee,

and was heavily involved in the planning for the shift of resources and people out of oncology. During this time, we produced three clinical candidates, a MEK inhibitor PD 0325901, which went through Phase I, and is still in clinical trials as of 2017, a CDK4/6-selective inhibitor PD 0332901, Palbociclib, which has been approved by the FDA for refractory ER+ breast cancer, and a second-generation pan-ErbB irreversible inhibitor, PF0299804 (Dacomitinib), which was evaluated in Phase 3 clinical trials for lung cancer, and is still in ongoing clinical trials as of 2017.

Interim Oncology Discovery Executive Director. July 2001-November 2001. After my predecessor stepped down from the position I was appointed as temporary Ann Arbor Oncology site head with overall responsibility for the site discovery oncology therapeutic area in a matrix system.

Director of Cancer Chemistry. January 2001-June 2003. During the therapeutic area alignment following the takeover of Parke-Davis by Pfizer, Metabolic Diseases were transferred to another PGRD site, and I was transferred back into the cancer group as Director of Cancer Chemistry. I had a group of 19 people reporting to me, and I was also responsible for managing co-ordination with 8 medicinal chemists working with us in Auckland, New Zealand. I was also a member of the Pfizer Global Oncology Team, which was responsible for coordinating strategy across the 3 sites where preclinical cancer research is carried out.

May 1992-June 2000 Parke-Davis Pharmaceutical Research Division
Address as below

Director of Diabetes Chemistry. May 1998-December 2000. I started up the chemistry group to support our diabetes project in May 1998 with three chemists reporting to me. I built the group up to sixteen chemists, looking for novel agents in the diabetes and obesity area. I was the Parke-Davis project coordinator, project leader and a member of the joint Research Council for the Parke-Davis/Ligand Pharmaceutical collaboration to find novel estrogenic agents. I was also a member of the Research Management Committee in the Parke-Davis/Allergan Inc. joint venture to find novel retinoids with anti-diabetic activity.

I returned to Parke-Davis as an *Associate Research Fellow*, in 1992, and became a part of the anti-cancer project, using the latest advances in signal transduction to find original, mechanism based, therapies. I was promoted to *Research Fellow* in April 1996. I have been involved in designing and synthesizing very potent and specific tyrosine kinase inhibitors, culminating in low picomolar inhibitors of the EGFR tyrosine kinase, an improvement of 105 in potency over our original leads. This work was very influential in demonstrating that truly selective potent inhibitors of tyrosine kinases could be obtained, and at the highly conserved ATP-binding site. I was also heavily involved in developing very selective, irreversible, inhibitors of the ErbB family of RTKs from our original leads, and the discovery and development of CI-1033, canertinib, our first clinical candidate. I also interacted strongly with our biology staff in getting new targets screened, and in coordinating strategy for both *in vitro* and *in vivo* screening. I have identified and defined leads from kinase random screens. I was the first person to identify the prototypical selective MEK inhibitor PD 098059 from random screening, and I was Chairman of the MAP kinase working group, (1994-1998) where we developed selective, nanomolar potency, inhibitors for the enzyme MEK, including two clinical candidates CI-1040 and PD 0325901.

November 1988-May 1992 Eisai Research Institute of Boston
4 Corporate Drive
Andover, MA 01810

Senior Scientist. I was one of four senior chemists, who along with four senior biologists ran the Institution under the guidance of Professor Y. Kishi. I supervised two junior chemists and one PhD chemist. My initial

work at Eisai was as a part of a larger team, working on antagonists for bacterial liposaccharides as a septic shock therapy. Then, for two years I led the chemistry of our urokinase inhibitor program, for evaluation of therapy in the anti-cancer and inflammation areas. This project gave me the experience of developing a project from scratch, and led to a successful patent filing. The potency of our lead series was raised by more than one thousand-fold, leading to a 40 nM urokinase inhibitor with good inhibitory selectivity over t-PA and plasmin. During this work, the lithiation chemistry of aryl fluorides was further elucidated, and novel heterocyclic syntheses were developed utilizing this chemistry.

September 1984-November 1988

Parke-Davis Pharmaceutical Research Division
Warner-Lambert Corporation
2800 Plymouth Road
Ann Arbor, MI 48105

Initially I was hired as a *Senior Scientist*. My responsibilities included chemical coordination for antipsychotic evaluation in the Adenosine Receptors project. I was the lead chemist on the synthesis of the first potent, highly selective, adenosine A_{2a} receptor agonist, in a project involving innovative use of molecular modeling. In February 1987 I began working on quinolones in the Anti-infective project, and in March 1988 I was promoted to *Research Associate*. During this time, I developed innovative techniques for novel quinolone synthesis, including developing chemistry to exploit the ability of aryl fluorides to direct ortho-lithiation. I gained considerable experience interacting with both biochemists and pharmacologists, and at picking compounds for both primary and secondary screening for efficacy and liabilities. As a member of the Antipsychotic Project Team, and the planning teams for two clinical candidates, I gained exposure to the requirements of chemical and product development, and toxicological and clinical evaluation. I also successfully developed chemical series to optimize receptor affinity and selectivity and *in vivo* profiles.

August 1978-August 1984

Department of Chemistry
Northern Illinois University
DeKalb, IL 60115

I was an Assistant Professor of Organic Chemistry, and was recommended for tenure and promotion to Associate Professor in November 1983. During this time, I taught the introductory 1 semester organic chemistry course four times, the non-majors' introductory one-year course twice, the chemistry majors' introductory one-year course organic course twice, and the graduate organic synthesis course twice. I also taught the first semester of the non-majors' one-year course three times during summer sessions. I successfully supervised two PhD students and two MS students. My research involved the synthesis and reactions of sulfur, silicon and phosphorus substituted allenes and dienes, with an emphasis on cycloadditions.

SCIENTIFIC SOCIETY MEMBERSHIP AND ACADEMIC AFFILIATIONS

Royal Society of Chemistry
American Chemical Society
Sigma Xi
American Association for the Advancement of Science
American Association for Cancer Research
Adjunct Assistant Professor, Department of Chemistry, Wayne State University 1996-present
Adjunct Associate Professor, School of Pharmacy, University of Michigan 2000-present
I lecture on Obesity and Diabetes in MedChem 533 in the graduate program in the UM College of Pharmacy, and I have been the external examiner on several Wayne State PhD committees.

CONSULTANCIES AND LEGAL EXPERIENCE

I have been a paid scientific consultant to at least twenty pharmaceutical companies, and I have carried out in excess of fifty Due Diligences for clients, frequently covering the pharmacology as well as the chemistry-related portions of the exercise. I have also helped with both Manufacturing Chemistry and Medicinal Chemistry for several clients, and have been named as an inventor on a number of patent applications as a result. I have written mainly or in total at least half a dozen patent applications for clients as a consultant. I have also been involved as a principal or consultant in four start-up companies, which either failed to obtain funding in the 2008-2012 recessionary period, or where we could not successfully duplicate the key findings in an external laboratory.

As an expert witness, I have written and had submitted to clients and/or courts over a dozen affidavits or expert reports to date. I have been deposed in the United States, Canada, and India, and I have appeared as an expert witness in the successful defense of a patent in a court trial in the USA.

PUBLICATIONS

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PRESENTATIONS AND ABSTRACTS

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EXHIBIT 2

List of Patent Cases March 2013-March 2018

The following were as an Expert witness, and I have had no follow-on work after writing an Expert Report.

For Aventis Pharmaceuticals Int. vs BDR Pharmaceuticals International at Indian Patent Office IP Appellate Board. ORA/38/2014/PT/DEL/2170.
For Aventis Pharmaceuticals Int. vs Intas Pharmaceuticals at Indian Patent Office IP Appellate Board. ORA/38/2014/PT/DEL/7831.
For Aventis Pharmaceuticals Int. vs Fresenius Kabi at Indian Patent Office IP Appellate Board. ORA/38/2013/PT/DEL/???. (All three were for same Indian patent)

For Bayer Healthcare LLC. (and Onyx Pharmaceuticals Inc). vs Mylan Inc. Civil Action No. 1:15-cv-114 in US District Court Delaware.

For Pharmacyclics Int. vs Laurus Labs Pvt Ltd at Indian Patent Office IP Appellate Board. Post-grant opposition to IN 262968.

For BMS vs NATCO. Delhi High Court. CS (OS) NO. 2279 of 2009
For BMS vs BDR Pharmaceuticals International Delhi High Court CS (OS) NO. 679 of 2013
For BMS in European Patent Office. 04 758 053.5 – 2123/ 1 610 780/ Ref M52088-OPPO

For this set of lawsuits, I wrote am expert report, and I was deposed, and I was prepped for trial, but the defendants pulled out at the beginning of the trial.

For Novartis Pharmaceuticals Corp, Mitsubishi Tanabe Pharma and Mitsui Sugar Co vs HEC Pharma Co. Civil Action No. 15-151-LPS in US District Court Delaware.
For Novartis Pharmaceuticals Corp, Mitsubishi Tanabe Pharma and Mitsui Sugar Co vs Ezra Ventures. Civil Action No. 15-150-LPS in US District Court Delaware.

For F. Hoffmann La Roche and OSI Pharmaceuticals vs Accura Care Pharmaceuticals. Delhi High Court CS (OS) NO. 1935 of 2011.
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For F. Hoffmann La Roche and OSI Pharmaceuticals vs Glenmark Pharmaceuticals Ltd. Delhi High Court CS (OS) NO. 402 of 2010.
For F. Hoffmann La Roche and OSI Pharmaceuticals vs Innovia Life Sciences. Delhi High Court CS (OS) NO. 1936 of 2011.
For F. Hoffmann La Roche and OSI Pharmaceuticals vs Oncare Life Sciences. Delhi High Court CS (OS) NO. 2459 of 2011.

For the following two cases, I have written an expert report, and I have been deposed in the Delhi High Court.
For F. Hoffmann La Roche and OSI Pharmaceuticals vs Natco Pharma Ltd. Delhi High Court CS (OS) NO. 2465 of 2009.

For F. Hoffmann La Roche and OSI Pharmaceuticals vs Dr Reddy's Laboratories. Delhi High Court CS (OS) NO. 81of 2010.

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